Differences in trigger factors and symptoms between patients with asthma-like symptoms and patients with asthma: development of a basis for a questionnaire

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Abstract Patients with asthma-like symptoms but with negative asthma tests are often misdiagnosed as having asthma and treated as asthmatics. They describe their trigger factors and symptoms very similar to those of patients with asthma. The aim of the study was to analyze differences in symptoms and trigger factors between asthma-like patients and asthmatics in order to elaborate a basis for a questionnaire for epidemiological and clinical use. A questionnaire with 54 questions about trigger factors and 137 questions about symptoms was sent to 40 patients with asthma-like symptoms and 40 with asthma, all consecutively selected from patients referred to an out-patient clinic for asthma and allergy for investigation of suspected asthma. Data were analyzed statistically in two steps using multiple logistic regression analysis. Significant differences were seen in several trigger factors and symptoms after the first analysis. After the second analysis, seven out of the 54 trigger factors and 22 out of the 137 symptoms emerged as those that most significantly discriminated between the two patient groups. These trigger factors and symptoms can be the basis of a new questionnaire with high discriminating power. Before using it, it is important to evaluate the best combination of variables, add some demographic variables and to test the reliability and validity of this new questionnaire.

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INTRODUCTION

Patients reporting asthma-like symptoms without having positive asthma tests have been described in several studies (1–9). Hyperventilation (4) and a sensory airway hyperreactivity have been proposed as underlying mechanisms in this asthma-like disorder (8). Characteristic of this kind of patient is complaints of asthma-like symptoms such as cough, increased phlegm, difficulty in getting air and heavy breathing. Chemical irritants like tobacco smoke, perfumes and exhaust gases and physical exercise, cold air or mental stress often trigger the symptoms. In patients in whom the diagnosis is based only on the history, the patient may receive the diagnosis asthma, as the symptoms are very similar. However, a proper clinical examination with asthma tests such as forced expiratory volume in one second (FEV_1), peak expiratory flow rate (PEFR), tests of reversibility and variability and a methacholine challenge test will show that these patients do not have any objective signs of bronchial asthma. Steroids, β_2-stimulants and other pharmacological treatment seem to have no or only slight effect. The prevalence in the general population of this asthma-like disorder is not yet known but it is estimated to 1% from studies performed in patients with asthma (5). Therefore, there is a need for a questionnaire that can be used in epidemiological studies. There is also a need for a questionnaire that can be used in the clinical setting for diagnostic purposes complementary to the lung function tests.

The aim of the present study was to analyze differences in symptoms and trigger factors between patients with asthma-like symptoms and patients with asthma in order to elaborate a basis for a questionnaire for epidemiological and clinical use.

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MATERIAL AND METHODS

Conduct of the study

First a self-administered, structured questionnaire including 54 trigger factors and 137 symptoms was constructed. This questionnaire was sent to 80 well-diagnosed, consecutively selected patients, 40 with asthma-like symptoms and 40 with asthma. Data collected from these patients were analyzed statistically in two steps using multiple logistic regression analysis in order to find those trigger factors and symptoms that most significantly discriminated between the groups. The statistical analysis resulted in a basis for a new questionnaire with seven trigger factors and 22 symptoms.

Construction of the questionnaire that was sent to the patients

The questionnaire sent to the patients consisted of 191 questions and was constructed in three steps as follows. First, records from 300 patients, not included in this study, referred to the clinic for investigation of suspected asthma was studied. The focus was specifically on how the patients had described their trigger factors and symptoms in structured questionnaires, used continuously in the clinic for the diagnosis of suspected asthma. In order also to capture the patients' own descriptions of the symptoms and trigger factors, open-ended questions and semi-structured interviews used in earlier research were studied as well (1–4).

Thereafter, the new questionnaire with altogether 191 questions (54 questions about trigger factors and 137 questions about symptoms) was constructed. The questions about trigger factors were grouped in five subsets related to: weather (11 items), physical activity (seven items), psychological stress (four items), odors (20 items) and dust (12 items). The patients were asked to estimate the severity of the trigger factors on a five-point Likert scale. The scale was graded: not at all, some, rather a lot, very much, extremely much. The questions about symptoms were grouped in twelve subsets related to: eyes (seven items), upper airways and nose (10 items), upper airways and throat (18 items), lower airways and chest (28 items), cough (eight items), stomach (seven items), skin (six items), sleep (10 items), tiredness (four items), infections (eight items), general symptoms (21 items) and pain (10 items). The patients were asked to estimate the frequency of the symptoms on a five-pointed Likert scale. The scale was graded: never, occasionally, once a month, once a week and daily. The patients were also asked to fill in unstructured comments in connection with each question.

Finally, before the questionnaire was sent to the patients, it was checked by a reference group of ten persons (doctors, nurses and one physiotherapist) all with several years of clinical experience of both categories of patients.

Patients

The questionnaire was sent to 80 well-diagnosed patients, 40 with asthma-like symptoms and 40 with asthma. Both groups were consecutively selected from patients referred to an outpatient clinic for asthma and allergy for investigation of suspected asthma. They were all diagnosed by doctors specialized in asthma and allergy.

For inclusion in the asthma-like group (AL-group), the patients were required to have negative asthma tests i.e. the following criteria had to be met:

(1) normal FEV_1 or PEFR values before inhalation of a β_2-stimulant defined as $>95\%$ of predicted normal value;
(2) lack of reversibility, defined as an increase of the FEV_1 or PEFR values after inhalation of salbutamol 0·8 mg $<10\%$;
(3) variability $<20\%$ of the PEFR values, measured morning and night for 14 consecutive days;
(4) a negative methacholine challenge test defined as $PC_{20} \geq 8$ mg ml (10);
(5) a negative skin prick test;
(6) no other disease that could have an impact on respiratory function;
(7) no current smoking;
(8) symptoms reported for at least 2 yrs.

To be included in the asthma group (A-group), at least two of the following four criteria had to be fulfilled:

(1) reversibility of the FEV_1 or PEFR values $\geq 15\%$ after inhalation of 0·8 mg salbutamol (11);
(2) FEV_1 or PEFR $\leq 80\%$ of predicted normal values before and $>90\%$ after inhalation of a β_2-stimulant;
(3) a positive methacholine challenge test defined as $PC_{20} \leq 4$ mg ml (10);
(4) variability $\geq 20\%$ of the PEFR values, when measured morning and night for 14 consecutive days (11).

A standardised methacholine test was used (10). To be allowed to start the test, FEV_1 had to be at least 65% of predicted value. No bronchodilators were allowed during a period of 4 h (short-acting) or 12 h (long-acting) before challenge. The patient inhaled NaCl for 2 min, the FEV_1 value after NaCl being the baseline. The challenge started with the concentration 0·03 mg ml^{-1}. Double doses were inhaled during two minutes with an interval of 5 min until the fall in FEV_1 was $>20\%$ or the maximum dose (16 mg ml^{-1}) was reached. The FEV_1 was recorded two and four minutes after the end of each inhalation. Results were expressed as PC_{20} (the concentration corresponding to 20% fall in FEV_1). In the present study

Table 1. Characteristics of the patient groups

Group	Sex male/female	Age, years median (range)	FEV_1 before β_2 % predicted mean (±SD)	FEV_1 after β_2 % predicted mean (±SD)	Duration of disorder, years, median (range)	Smoking never/ ex-smoker	Skin prick test neg/pos
AL	7/33	41 (20–63)	108 (11·3)	110(11·2)	12(2–50)	32/8	40/0
A	7/33	43 (21–67)	82 (14·4)	95(12·0)	15(2–53)	29/11	17/22

29 of the patients with asthma-like symptoms had a methacholine test with a $PC_{20} > 16$ mg ml^{-1}, 10 patients > 16 and one ≥ 8. In the asthma group, 15 had a methacholine test with a PC_{20} varying between 0·1 and 4 mg ml^{-1}.

All patients reported breathing-related symptoms. In the AL-group 35% (14/40) reported having symptoms daily, 45% (18/40) sometimes and 20% (8/40) on single occasions. In the A-group the corresponding figures were 30% (12/40), 35% (14/40) and 35% (14/40). For further characteristics of the patients see Table 1.

Thirty-seven (93%) of the patients in the AL-group were prescribed a β_2-stimulant. Twenty-four (60%) took the medicine, but only two thought that it had any effect. None was prescribed corticosteroids. All the patients in the A-group (100%) were prescribed a β_2-stimulant. They all took their medicine and 25 (63%) of them thought that it had effect. Twenty-six (65%) were prescribed inhaled corticosteroids (one orally) on a regular basis.

The Ethics Committee of Göteborg University approved the study.

Statistical methods

Comparisons between the two patient groups were first performed with Fisher's permutation test (12–13) with respect to all the 191 items (trigger factors and symptoms) of the questionnaire. Thereafter, the 101 items that differed significantly between the two groups were grouped into 17 subsets. The items within each subset reflected similar aspects. For each subset of items, a stepwise logistic regression analysis was applied (14). Before the second step of the analysis, the number of trigger factors and symptoms was reduced to 17 and 52 respectively items by choosing representatives for each subset. In this reduction, the following criteria were used: (1) Each subset was to be represented by at least one trigger factor or symptom. Subsets with many items (e.g. odours, general factors) should be represented by more items than subsets with few items (e.g. weather) but not more than 10; (2) If within the subset two items described the same phenomenon, the one that was most representative and had the lowest significance level was chosen (e.g. of the psychological items 'anxiety', 'mental strain' and 'conflicting situations and experiences', conflicting situations and experiences was chosen); (3) Items that were diffuse (e.g. 'earth', 'leather' etc.) so that you really do not know what they measure were omitted. The items remaining significant discriminators between the groups in the series of multiple analyses can be used to construct a new questionnaire with high discriminating power. $P < 0{\cdot}05$ was considered significant.

Odds ratios and 95% confidence intervals are given in Tables 2 and 3. They can be interpreted when comparing two patients with exactly the same values of all variables except the current one, where the patient corresponding to the numerator is assumed to have one unit higher value compared to the patient in the denominator. If the β-coefficient is positive, a higher value of the respective variable is associated with a higher risk of having asthma. Conversely, if the β-coefficient is negative, a higher value of the variable is associated with a lower risk of having asthma. For example, the odds ratio for the trigger factor 'warm and dry weather' is 0·33. This means that the probability of having asthma is about 67% lower for a patient compared to another one if the first patient has one unit higher value of this trigger factor but is similar with respect to all other variables of importance. One unit higher value is attained if the answer to the question about warm and dry weather is 'some' instead of 'not at all', 'rather a lot' instead of 'some', and so on.

RESULTS

All who agreed to join the project also completed it. The unstructured comments did not add any new information to the study and are therefore not reported.

Trigger factors

After the first statistical analysis, a significant difference was seen between the two patient groups in 29 (54%) of the 54 trigger factors. The mean ratings of the AL-group were significantly higher in all these 29 trigger factors compared to those of the A-group. See Table 2, column 2 (first step P-value). In one subset of trigger factors,

Table 2. Differences $P < 0{\cdot}05$ between the AL-group and the A-group in their ratings of trigger factors

Subsets of Trigger factors and trigger factors	First step *P*-value	Second step *P*-value	Second step β coefficient	Second step odds ratio (95%CI)
Weather				
Warm weather	0·0002	omitted	–	
Warm/dry weather	0·0006	0·0015	−1·1072	0·33 (0·17, 0·65)
Warm/damp weather	0·0431	omitted	–	–
Psychological			–	–
Anxiety	0·0188	omitted	–	–
Mental strain	0·0033	omitted	–	–
Conflicting situations and experiences	0·0006	0·0012	−0·7056	0·49 (0·32, 0·76)
Odours				
Perfume	0·0005	NS	–	–
After shave	0·0016	NS	–	–
Detergent	0·0042	NS	–	–
Cleanser	0·0169	omitted	–	–
Hairspray	0·0001	0·0002	−0·7155	0·49 (0·34, 0·71)
Printer's ink	0·0435	omitted	–	–
Colour paint	0·0045	omitted	–	–
Glue	0·0355	omitted	–	–
Plastic	0·0294	omitted	–	–
Leather	0·0121	omitted	–	–
Exhaust gases	0·0050	0·0056	−0·5072	0·60 (0·42, 0·86)
Mould	0·0100	omitted	–	–
Earth	0·0194	omitted	–	–
Flowers	0·0177	NS	–	–
Stuffy air	0·0035	0·0385	−0·4817	0·62 (0·39, 0·97)
Smell from cooking	0·0085	NS	–	–
Smell from tobacco	0·0035	0·0038	−0·5179	0·60 (0·42, 0·85)
Smell from open fire	0·0035	NS	–	–
Dust			–	–
Bad ventilation	0·0060	NS	–	–
Room with mould	0·0029	NS	–	–
Dust from paper	0·0226	NS	–	–
Dust from detergent	0·0046	0·0058	−0·5260	0·59 (0·41, 0·86)
Dust from cloth	0·0320	NS		

'Physical activity', no significant differences were seen between the patient groups and is therefore not presented in the Table.

In the second analysis, 17 of the 29 trigger factors in which a significant difference between the patient groups had been found were included. The remaining 12 trigger factors were omitted. Regarding this procedure see 'Methods'. Seven of the 17 trigger factors turned out to be the most significant discriminating trigger factors between the two patient groups. See Table 2, columns 3–5 (second step *P*-value, β coefficient, odds ratio).

Symptoms

After the first statistical analysis, a significant difference was seen between the ratings of the frequency of symptoms in 72 (53%) of the 137 symptoms. The mean ratings of the A-L group were significantly higher in all the 72 symptoms except for 'wheezing' and 'hissing'. See Tables 3a and 3b, column 2 (first step *P*-value). No significant differences between the patient groups were found in the variables that belonged to the subset 'Skin'. This subset is therefore not presented in the Table.

In the second analysis, 52 of the 72 symptoms in which a significant difference between the patient groups had been found were included. The remaining 20 symptoms were omitted. Regarding this procedure see 'Methods'. Twenty-two of the 52 symptoms emerged as those, which discriminated most significantly between the two patient groups. See Tables 3a and 3b, columns 3–5 (second step *P*-value, β coefficient, odds ratio).

Table 3a. Differences $P < 0{\cdot}05$ between the AL-group and the A-group in their ratings of symptoms

Subsets of symptoms and symptoms	First step *P*-value	Second step *P*-value	Second step β coefficient	Second step odds ratio (95%CI)
Eyes				
Itching	0·0363	NS	–	–
Dryness	0·0058	0·0084	−0·5279	0·59 (0·40, 0·87)
Running eyes	0·0493	omitted	–	–
Blurred vision	0·0052	NS	–	–
Upper airways-nose				
Itching	0·0016	NS	–	–
Nasal congestion	0·0177	NS	–	–
Feeling of swelling in the nose	0·0085	omitted	–	–
Dry mucus	0·0000	0·0187	−0·4960	0·61 (0·40, 092)
Sensitivity to odours	0·0000	0·0123	−0·5155	0·60 (0·40, 0·89)
Pain in sinuses	0·0019	NS	–	–
Upper airways-throat				
Itching	0·0327	NS	–	–
Irritation	0·0022	NS	–	–
Dry mucous	0·0004	0·0176	−0·4715	0·62 (0·42, 0·92)
Need to clear one's throat	0·0224	NS	–	–
Difficulty in swallowing due to a lump	0·0062	NS	–	–
Taste of blood	0·0000	0·0033	−1·5129	0·22 (0·08, 0·60)
Lower airways-chest				
Difficulty in getting air	0·0158	0·0020	−0·9955	0·37 (0·20, 0·69)
Difficulty in getting oxygen	0·0061	NS	–	–
Need to take deep breaths	0·0337	NS	–	–
Difficulty in taking deep breaths	0·0291	0·0192	−0·7233	0·49 (0·26, 0·89)
High costal breathing	0·0383	omitted	–	–
Whistling in chest	0·0000	omitted	–	–
Wheezing	0·0002	0·0000	1·7235	5·60 (2·46, 12·75)
Hissing	0·046	0·0066	0·9748	2·65 (1·31, 5·36)
Feeling of a tight chest	0·0063	omitted	–	–
Pressure over chest	0·0005	NS	–	–
Feeling of sore airways	0·0082	0·0029	−1·0745	0·34 (0·17, 0·69)
Burning, sore airways	0·0241	omitted	–	–
Cough				
Dry cough	0·0071	NS	–	–
Irritating cough	0·0038	0·0046	−0·5458	0·58 (0·40, 0·85)
Stomach				
Nausea	0·0000	0·0002	−1·2644	0·28 (0·15, 0·55)
Need to vomit	0·0004	NS	–	–
Belching	0·0211	omitted	–	–
Heartburn	0·0361	omitted	–	–
Flatulence	0·0024	omitted	–	–
Diarrhoea	0·0493	omitted	–	–
Sensation of bloated abdomen	0·003	0·0305	−0·4219	0·66 (0·45, 0·96)

DISCUSSION

The present study shows that patients with asthma-like symptoms and patients with asthma describe their trigger factors and symptoms very similarly. By using multiple logistic regression analysis, seven out of 54 trigger factors and 22 out of 137 symptoms were identified as those that most significantly discriminate between the two patient groups. Of the trigger factors, 'warm and dry weather' was the most discriminating one. The most discriminating symptoms were 'wake up due to nasal congestion', 'a sore throat', 'feeling of confusion' 'feeling of tenseness in the body', 'taste of blood', 'wheezing', 'hissing', 'feeling of sored airways' and 'nausea'.

The patients were selected on strict criteria, used in earlier studies (1–5). The two patient groups had been referred to a specialist clinic for asthma and allergy and are therefore not representative of all patients with asthma-

Table 3b. Differences $P < 0{\cdot}05$ between the AL-group and the A-group in their ratings of symptoms

Subsets of symptom and symptoms	First step *P*-value	Second step *P*-value	Second step β coefficient	Second step odds ratio (95%CI)
Sleep				
Sleeping problems	0·0376	omitted	–	–
Difficulty in getting to sleep	0·0019	NS	–	–
Wake up several times during night	0·0246	NS	–	–
Wake up early	0·0239	NS	–	–
Wake up due to nasal congestion	0·0000	0·0002	−1·1059	0·33 (0·18, 0·60)
Tiredness				
Abnormal general tiredness	0·0040	omitted	–	–
Abnormal tiredness/weakness after physical exertion	0·0317	omitted	–	–
Abnormal tiredness/weakness after psychological stress	0·0015	0·0024	−0·5962	0·55 (0·37, 0·81)
Infection/inflammation				
A sore throat	0·0014	0·0047	−1·4209	0·24 (0·09, 0·65)
General				
Headaches	0·0013	0·0328	−0·5905	0·55 (0·32, 0·95)
Dizzieness	0·0140	NS	–	–
Balance problems	0·0120	omitted	–	–
Fumbling	0·0010	NS	–	–
Feeling of confusion	0·0000	0·0091	−0·9993	0·37 (0·17, 0·78)
Palpitations	0·0060	NS		
Cold hands and feet	0·0023	0·0384	−0·3602	0·70 (0·50, 0·98)
Feeling of chilliness	0·0154	omitted	–	–
Feeling of warmth in the body	0·0084	omitted	–	–
Anxious feelings	0·0011	NS	–	–
Feelings of panic	0·0478	omitted	–	–
Stiffness in fingers and arms	0·0130	NS	–	–
Tingling fingers and hands	0·0033	NS	–	–
Loss of sensibility in the face	0·0238	omitted	–	–
Stiffness around the mouth	0·0105	NS	–	–
Feeling of tenseness in the body	0·0000	0·001	−1·3366	0·26 (0·13, 052)
Feeling of illness	0·0003	NS	–	–
Irritated	0·0021	NS	–	–
Difficulty in concentrating	0·003	0·0090	−0·7037	0·49 (0·29, 0·84)
Pain				
Pain in the chest	0·0036	NS	–	–
Tender to touch in the chest	0·0030	0·0050	−0·6511	0·52 (0·33, 0·82)
Aches in the whole body	0·0118	NS	–	–
Pain/muscle cramp in chest	0·0210	omitted	–	–
Pain/cramp between shoulder blades	0·0151	omitted	–	–
Aches in the joints	0·0244	NS	–	–
Aches in the airways	0·0024	NS	–	–

like symptoms or asthma. However, it is an advantage that all the patients in this study were diagnosed by a few doctors, specialized in asthma and allergy, all with long clinical experience of both patient groups.

Out of 54 trigger factors and 137 symptoms, the patients of the asthma-like group rated the severity of 29 trigger factors and the frequency of 72 symptoms significantly higher than the patients of the asthma group. Why? One explanation might be that the patients with asthma-like symptoms, wise from earlier experience, felt that they had to enhance when answering questions/questionnaires in order to be believed, as their asthma tests are negative. However, in the present study the asthma-like patients had already had received their 'diagnosis' at the clinic and were thus confirmed in this respect. Another and more likely explanation is that the patients with asthma-like symptoms in fact experience more serious problems than the patients with asthma.

It should be noted that in the final analysis the subsets 'Physical activity' and 'Skin' are not represented, as no significant differences were found between the two patient groups. Both patient groups rated physical activity high.

On a five-pointed scale, they both scored on average between three and four, corresponding to the categories 'rather a lot' and 'very much' for running and jogging. It is well known that exercise is a trigger of asthma and it is therefore surprising that no significant differences were found between the groups. However, the finding is supported by two earlier studies (2,9). Regarding the subset 'Skin', both groups scored on average between two and three, corresponding to the categories 'occasionally' and 'once a month'.

Among the symptoms that remained as significant discriminators between the two patient groups, there are symptoms not only representing the eyes and upper and lower airways but also other organic systems, sometimes described as 'general symptoms'. It has been found in earlier studies that both categories of patients suffer from several 'general symptoms' but the asthma-like patients to a higher degree and more frequently (1,3). The 'general' symptoms, described by the asthma-like patients, may be overlooked if too much attention is paid the airways problems. Moreover, the patient may not always mention these symptoms, as he or she may not think that this is relevant information or what the doctor is interested in. The results of this study illustrate the importance of being open-minded and listening to how the patients describe their disorder in their own words.

Patients with asthma-like symptoms but with negative asthma tests have been described only for the past 10 years. As this 'diagnosis' is not generally recognized, there is a risk that this kind of patient is still diagnosed and treated from an asthma perspective. We also see that patients referred to our clinic for investigation of asthma have often been improperly diagnosed as asthmatics. This may happen if the diagnosis is based solely on the history and not on proper lung function tests, as the descriptions of symptoms and trigger factors are quite similar. Likewise, it is very important not to diagnose a patient as asthma-like without having seen that the asthma tests are negative. In future, for diagnostic purposes, it would be valuable also to add data on makers of inflammation, such as blood eosinophils.

Due to lack of suitable diagnostic instruments, the prevalence of subjects suffering from asthma-like symptoms but with negative asthma tests has not yet been studied. From studies in patients with asthma, the prevalence of asthma-like symptoms has been estimated to 1% in an adult population aged 35–36, 50–51 and 65–66 years (15). Using multiple logistic regression analysis, the present study shows that seven trigger factors and 22 symptoms can later be used as significant discriminators between the patient groups when constructing a questionnaire with high discriminating power for epidemiological use for the study of the prevalence of asthma-like symptoms in large populations. Before this is done, an evaluation of the best combination of variables must be made and other variables must be added for example demographic variables, how the disorder has developed and it's diurnal and seasonal variations. The questionnaire may also be used as a diagnostic instrument complementary to lung function tests in the clinical setting, but first it must be tested with regard to reliability and validity. This work is now in progress.

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